filed June 30, 1994, which issued as U.S. Patent 5,538,982 on July 23, 1996; which is a divisional of Application No. 07/946,635, filed on September 18, 1992, which issued as U.S. Patent 5,360,820 on November 1, 1994; the entire contents of which are hereby incorporated by reference and for which priority is claimed under 35 U.S.C. § 120; and this application claims priority of Application Nos. 91 20172.3; 92 02839.8; and 92 04151.6 filed in Great Britain on September 20, 1991; February 11, 1992; and February 27, 1992, respectively, under 35 U.S.C. § 119.--

REMARKS

The specification has been amended to update the status of the parent application, which is now patented.

Applicants respectfully request that an interference be declared under the provisions of 35 U.S.C. § 135 between the above-identified Application No. 09/986,679 and U.S. Patent 5,576,317 (hereinafter referred to as the Pfizer '317 patent), which issued on November 19, 1996, and is assigned to Pfizer Inc. of New York, New York.

Applicants herein present the following facts in compliance with 37 C.F.R. § 1.607. The following paragraph numbers correspond to the paragraph numbers of § 1.607(a).

(1) Applicants request an interference with U.S. Patent 5,576,317.

(2) The Proposed Counts for the interference are as follows:

PROPOSED COUNT 1

A pharmaceutical composition for the treatment or prevention of emesis comprising a $5HT_3$ receptor-antagonist, an NK-1 receptor antagonist and a pharmaceutically acceptable carrier.

OR

A method of treating or preventing emesis in a mammal, comprising administering to said mammal an anti-emetic effective amount of a pharmaceutical composition comprising a $5HT_3$ receptor antagonist, an NK-1 receptor antagonist and a pharmaceutically acceptable carrier.

OR

A method of treating or preventing emesis in a mammal, comprising administering to said mammal a $5HT_3$ receptor antagonist and an NK-1 receptor antagonist in amounts that render the combination of such two active agents effective in the treatment or prevention of such disorder.

PROPOSED COUNT 2

A pharmaceutical composition for the treatment or prevention of emesis comprising a $5HT_3$ receptor-antagonist selected from the group consisting of ondansetron, tropisetron, granisetron and metclopramide, an NK-1 receptor antagonist and a pharmaceutically acceptable carrier.

OR

A method of treating or preventing emesis in a mammal, comprising administering to said mammal an anti-emetic effective amount of a

pharmaceutical composition comprising an NK-1 receptor antagonist and either ondansetron, tropisetron, granisetron and metclopramide.

OR

A method of treating or preventing emesis in a mammal, comprising administering to said mammal a $5HT_3$ receptor antagonist selected from the group consisting of ondansetron, tropisetron, granisetron and metclopramide and an NK-1 receptor antagonist in amounts that render the combination of such two active agents effective in the treatment or prevention of such disorder.

(3) Claim 1 of the Pfizer '317 patent corresponds exactly to the first alternative of Proposed Count 1, claim 4 of the Pfizer '317 patent corresponds exactly to the second alternative of Proposed Count 1, and claim 7 of the Pfizer '317 patent corresponds exactly to the third alternative of Proposed Count 1. Claims 3, 5, 8, 9, 10, 12, 13 and 14 of the '317 patent also correspond to Proposed Count 1.

Claims 2, 6 and 11 of the '317 patent correspond to proposed Count 2.

(4) Claim 11 of the present '679 application corresponds exactly to the first alternative of Proposed Count 1. Claim 14 of the present '679 application corresponds exactly to the second alternative of Proposed Count 1. Claim 16 of the present '679 application corresponds exactly to the third alternative of Proposed Count 1.

Claims 3, 12, 15 and 19 of the '679 application correspond to Proposed Count 2.

It is to be noted that claim 1 in the present '679 application corresponds exactly to claim 18 of parent Application No. 08/706,836, which was filed on September 3, 1996. Claim 1 of the present application (and therefore claim 18 of the parent '836 application) corresponds substantially to claim 4 of the Pfizer '317 patent except that present claim 1 recites that the NK_1 antagonist is used in combination with a systemic anti-inflammatory corticosteroid or $5HT_3$ antagonist. Thus, although claim 1 of the present '679 application varies slightly in wording from claim 4 of the Pfizer '317 patent, these claims have substantial overlap and are directed to the same invention. Therefore, claim 1 of the present '679 application corresponds to Proposed Count 1.

Claim 3 of the present '679 application, claim 20 in the parent '836 application and claim 6 of the Pfizer '317 patent (which all correspond to Proposed Count 2) substantially overlap since two of the recited NK-1 receptor antagonists (i.e., ordansetron and granisetron) are identical. Therefore, these claims are directed to the same invention and correspond to Proposed Count 2.

Claims 2 and 4-10 in the present '679 application correspond exactly to claims 19 and 21-27, respectively, in the parent '836 application, the latter claims having been submitted to the USPTO on

September 3, 1996, prior to the issuance of the Pfizer '317 patent on November 19, 1996.

(5) All of the terms which appear in any application claim corresponding to Proposed Counts 1 and 2 are present in the disclosure of the '679 application and also in the parent '836 application. Appendix A, attached hereto, applies the terms of claims 1 and 3 (corresponding to Proposed Counts 1 and 2) to the disclosure in the present '679 application as well as the disclosure in the parent '836 application.

(6) Applicant submits that the claims of the present '679 application, which correspond to Proposed Counts 1 and 2, do not violate 35 U.S.C. § 135(b). 35 U.S.C. § 135(b) provides in relevant part:

> "A claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made *prior to one year* from the date on which the patent was granted . . ." *(emphasis added)*.

This provision requires an applicant to present "conflicting claims" prior to one year from the date of patent issuance.

The Pfizer '317 patent issued on November 19, 1996. The applicant herein presented claims substantially the same as the claims in the Pfizer patent in parent Application No. 08/706,836 on September 3, 1996. The applicant subsequently cancelled the "conflicting claims" from the application during *ex parte* prosecution on May 22, 1997 (after issuance

of the '317 patent). However, the original presentation of the "conflicting claims" occurred during the pendency of the Pfizer application and before the Pfizer '317 patent issued. These claims were also present in the '836 application after the Pfizer '317 patent issued. Applicant has reintroduced these previously cancelled "conflicting claims" in the present application.

Such reintroduction of claims is permitted according to the decision in *Tezuka, et al. v. Wilson, et al.*, 224 USPQ 1030 (Bd. Pat. App.s Int. 1984), which interprets the relevant statutory provision. Pursuant to *Tezuka*, Applicant is entitled to reintroduce the "conflicting claims" in the present divisional application even though the divisional application was filed on November 5, 2001, more than one year after the issuance of the Pfizer patent on November 19, 1996.

In the *Tezuka* case, the Board interpreted the words "prior to" in 35 U.S.C. § 135(b). The issue before the Board was whether Wilson had presented claims in his application for the same or substantially the same subject matter as *Tezuka*'s patent claims 1 to 3 prior to one year from the date on which the *Tezuka* patent was granted as required by 35 U.S.C. § 135(b). Wilson's parent application, filed on September 6, 1977, contained original claims 24-30, directed to a cement-forming liquid for use as a component of a poly(carboxylate) cement. These claims were cancelled on July 21, 1978, and were not reasserted in the parent application. These claims were then presented in Wilson's involved application filed on June 14, 1979, which was more than one

year after the issuance of the *Tezuka* patent on May 16, 1978. Claim 32 was also presented at this time as a substantial copy of *Tezuka*'s patent claim 1 in order to provoke an interference with Wilson. *Tezuka* argued that Wilson had not claimed the same or substantially the same subject matter as that claimed in the *Tezuka* patent within the time required by the statute. The Board held that Wilson had claimed substantially the same subject matter as that of *Tezuka*'s claims 1 to 3 prior to one year from the date on which the *Tezuka* patent was granted. The Board found that "the words 'prior to' in 35 U.S.C. § 135(b) point to a critical date prior to which the copier had to be claiming the invention. *It does not matter whether the claims are subsequently cancelled either before or after the issuance of the patent.*" (*id*, at 1036) *(emphasis added)*.

Like Wilson in the *Tezuka* case, the Applicant herein introduced the "conflicting claims" in the parent '836 application and subsequently cancelled them. In *Tezuka*, Wilson introduced the conflicting claims in an application that was filed one year after the issuance of the *Tezuka* patent. Likewise, the "conflicting claims" in the present '679 application were originally introduced in a parent application that was pending during the pendency of the Pfizer '317 patent.

Following the reasoning set forth in *Tezuka*, Applicant should be allowed to reintroduce the "conflicting claims" in the present divisional application and request an interference pursuant to 37 C.F.R.

§ 1.607, even though this divisional application was filed more than one year after the issuance of the Pfizer '317 patent.

Applicants are entitled to the benefit of all prior U.S. applications for proposed Counts 1 and 2, including Application No. 08/706,836, filed on September 3, 1996, which issued as U.S. Patent 6,326,383 B1 on December 4, 2001, which is a continuation of Application No. 08/579,294, filed on December 27, 1995, which issued as U.S. Patent 5,798,363 on August 25, 1998, which is a continuation of Application No. 08/269,079, filed June 30, 1994, which issued as U.S. Patent 5,538,982 on July 23, 1996, which is a divisional of Application No. 07/946,635, filed on September 18, 1992, which issued as U.S. Patent 5,360,820 on November 1, 1994.

Applicants are also entitled to the filing date of U.K. application 92 04151.6 for proposed Counts 1 and 2, which was filed on February 27, 1992. A copy of this application is attached hereto.

The Examiner is requested to refer in particular to the first full paragraph on page 14 of the U.K. application which reads as follows:

> The tachykinin antagonists may, if desired, be administered [in] combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the tachykinin antagonists may be administered in combination with a systemic anti-inflammatory corticosteroid such as methyl prednisolone or dexamethasone, or a $5HT_3$ antagonist such as ondansetron, granisetron or metoclopramide.

For the foregoing reasons, Applicant submits that all of the provisions of 37 C.F.R. § 1.607 have been met, and respectfully requests

that an interference be declared between the present '679 application and the Pfizer '317 patent.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number shown below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr. (Reg. No 28,977)
Raymond C. Stewart (Reg. No. 21,066)

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

RCS/GMM/las/kdm

Attachments:
Marked-up Version Showing Changes Made
Appendix A
U.K. Application No. 92 04151.6

MARKED-UP VERSION SHOWING CHANGES MADE

In the Specification:

The first paragraph on page 1 of the specification has been amended as follows:

This application is a [☐ continuation ☒] divisional [☐ continuation-in-part] of [co-pending] Application No. 08/706,836, filed on September 3, 1996, which issued as U.S. Patent 6,326,383 B1 on December 4, 2001, which is a continuation of Application No. 08/579,294, filed on December 27, 1995, [now] which issued as U.S. Patent 5,798,363 on August 25, 1998, which is a continuation of Application No. 08/269,079, filed June 30, 1994, [now] which issued as U.S. Patent 5,538,982 on July 23, 1996; which is a divisional of Application No. 07/946,635, filed on September 18, 1992, [now] which issued as U.S. Patent 5,360,820 on November 1, 1994; the entire contents of which are hereby incorporated by reference and for which priority is claimed under 35 U.S.C. § 120; and this application claims priority of Application Nos. 91 20172.3; 92 02839.8; and 92 04151.6 filed in Great Britain on September 20, 1991; February 11, 1992; and February 27, 1992, respectively, under 35 U.S.C. § 119.--

Appendix A

Claims in Application No. 08/706,836 (Parent Appln.)	Claims in Application No. 09/~~986~~985,679 (Present Appln.)	Disclosure in the '836 and '679 Applications which supports the corresponding claims.
18	1 (Proposed Count 1)	Page 1, lines 23-27; Page 2, lines 23-26; Page 22, lines 5-8; and Page 28, lines 18-25
20	3 (Proposed Count 2)	Page 22, lines 5-8; Page 28, lines 22-25

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit den in den Akten befindlichen Unterlagen der unten bezeichneten europäischen Patentanmeldung überein (Regel 94(4) EPÜ).

The attached is a true copy of documents contained in the European patent application indicated below (Rule 94(4) EPC).

Les documents ci-annexés sont conformes aux documents figurant dans le dossier de la demande de brevet dont le numéro est indiqué ci-dessous (règle 94(4) CBE).

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

92202831.1

München, d
Munich, 05/06/97
Munich,

Der Präsident des Europäischen Patentamts:
Im Auftrag.

For the President of the European Patent Office.

Le Président de l'Office européen des brevets
p.o.

H. Kuebart

Helga Kuebart

The Patent Office

The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

I, the undersigned, being an officer duly authorised in accordance with Section 62(3) of the Patents and Designs Act 1907, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the Patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 3rd September 1992

27 FEB 1992

THE PATENT OFFICE
27 FEB 1992
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applicant if such prohibition or
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dent in the United Kingdom are
o reminded that under Section 23,
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t less than 6 weeks previously in
e United Kingdom for a patent for
e same invention and either no
ection prohibiting publication or
mmunication has been given, or
y such direction revoked.

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

MEDICAMENTS

2 Applicant's details

☐ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
GLAXO GROUP LIMITED

Country *(and State of incorporation, if appropriate)*
GREAT BRITAIN

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX

UK postcode UB6 ONN
(if applicable)

Country GREAT BRITAIN

ADP number *(if known)* 5969647001 P.A.

e and 2f:
re are further applicants
e provide details on a separate
t of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases,** please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known) 00473587001

a address for service in the United
ngdom must be supplied.

Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ ***Please give details below***

Agent's name

C. L. BREWER / S. R. JAMES / W. A. FILLER

Agent's address

C/O GLAXO HOLDINGS P.L.C.
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD, MIDDLESEX

Postcode UB6 0NN

Agent's ADP number 5841499002.

b:
f you have appointed an agent,
ll correspondence concerning
our application will be sent to
he agent's United Kingdom
ddress.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

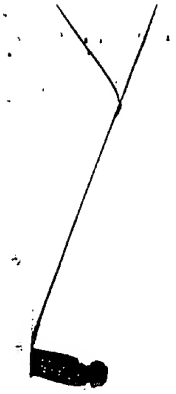
Name

Address

Postcode

ADP number
(if known)

Daytime telephone
number *(if available)*



4 Reference number

4 Agent's or applicant's reference number *(if applicable)* CLB/JV/CH181

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No [X] ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

ou are declaring priority from a T Application please enter 'PCT' the country and enter the country le (for example, GB) as part of the lication number.

ase give the date in all number mat, for example, 31/05/90 for 31 ay 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

nswer must be 'No' if:
applicant is not an inventor
re is an inventor who is not
applicant, or
applicant is a corporate
dy.

se supply duplicates of
(s), abstract, description
drawing(s).

se mark correct box(es)

or your appointed agent
Rule 90 of the Patents
s 1990) must sign this
est.

Please sign here

ompleted fee sheet should
erably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inven

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Fo 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	14
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9 Request

I/We request the grant of a patent on the basis of this application.

Signed C L Brewer Agent for the Applicant Date 27/02/1992 *(day month year)*

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

☐ *The Comptroller*
The Patent Office
Cardiff Road
NEWPORT
Gwent
NP9 1RH

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London
WC2A 1AY

CH181

MEDICAMENTS

The present invention relates to the use of tachykinin antagonists, including substance P and other neurokinin antagonists, in the treatment of emesis.

Tachykinin antagonists are known to be useful in the treatment of a variety of disorders including pain, inflammatory diseases, allergic disorders, CNS disorders, skin disorders, cough and gastrointestinal disorders such as ulcerative colitis and Crohn's disease.

It has now been found that tachykinin antagonists, including substance P and other neurokinin antagonists, are useful in the treatment of emesis.

The invention accordingly provides, in a first aspect, the novel use of tachykinin antagonists, including substance P and other neurokinin antagonists, in the treatment of emesis.

There is also provided as a further aspect of the invention the use of tachykinin antagonists, including substance P and other neurokinin antagonists, in the preparation of a medicament for use in the treatment of emesis.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to emesis , comprising administration of an effective amount of a tachykinin antagonist, including substance P and other neurokinin antagonists.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Tachykinin antagonists, including substance P and other neurokinin antagonists, have been shown to have anti-emetic activity as indicated by for example their ability to inhibit cisplatin-induced emesis in the ferret.

The treatment of emesis mentioned hereinbefore includes the treatment of nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. Tachykinin

antagonists, including substance P and other neurokinin antagonists are useful in the treatment of emesis however induced. For example emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; antimetabolites, e.g. cytarabine, methotrexate and 5-fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis; pregnancy; vestibular disorders, such as motion sickness; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; and decreased intercranial pressure (e.g. altitude sickness).

Tachykinin antagonists acting at NK_1 receptors have been found to be particularly useful in the treatment of emesis.

In a preferred aspect therefore the invention provides the use of an NK_1 receptor antagonist in the treatment of emesis.

Specific tachykinin antagonists for use in the present invention include those generically and specifically disclosed in the following patent specifications which disclosures are incorporated herein by reference:-

EP 0327009;

EP 0333174;

WO 91/12266;

EP 0284942;

GB 2216529;

US 4839465; and

WO 91/02745

Particularly preferred are the tachykinin antagonists disclosed in :-

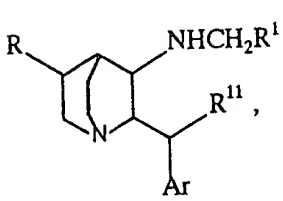
EP 0360390 in particular:

N-[N^1-[L-pyroglutamyl-L-alanyl-L-aspartyl-L-prolyl-L-asparaginyl-L-lysyl-L-phenylalanyl-L-tyrosyl]-4-methyl-1-oxo-2S-(6-oxo-5S-1, 7-diazaspiro[4. 4]non-7-yl)pentyl]-L-tryptophanamide and

N-[N^1-[L-arginyl-L-prolyl-L-lysyl-L-prolyl-L-glutaminyl-L-glutaminyl-L-phenylalanyl-L-phenylalanyl]-4-methyl-1-oxo-2S-(6-oxo-5S-1,7-diazaspiro[4. 4]nonan-7-yl)-pentyl]-L-tryptophanamide;

WO 90/05525

WO 90/05729 i.e. quinuclidine derivatives of the formulae:



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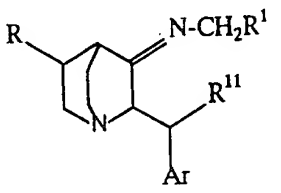
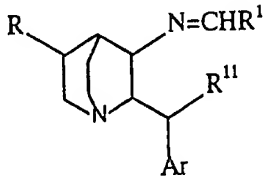


II

and



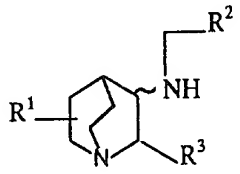
III

including the pharmaceutically acceptable salts thereof; wherein Ar is thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl; R is hydrogen or alkyl having from one to four carbon atoms; R^1 is cycloalkyl having from five to seven carbon atoms, norbornyl, pyrrolyl, 2,3-dihydrobenzofuranyl, thienyl, alkoxythienyl having from one to three carbon atoms in the alkoxy moiety, pyridyl, hydroxypyridyl, quinolinyl, indolyl, naphthyl, alkoxynaphthyl having from one to three carbon atoms in the alkoxy moiety, biphenyl 2,3-methylenedioxyphenyl, or phenyl optionally substituted with up to two substituents selected from cyano, nitro, amino, N-monoalkylamino having from one to three carbon atoms in the alkyl moiety, fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbons, alkoxy having from one to three carbon atoms, allyloxy,

hydroxy, carboxy, alkoxycarbonylbenzyloxy having from one to t carbon atoms in the alkoxy moiety, carboxamido or N, dialkylcarboxamido having from one to three carbon atoms in t alkyl moiety; and R^{11} is branched chain alkyl having from thre four carbon atoms, branched chain alkenyl having from five to six carbon atoms, cycloalkyl having from five to seven carbon atoms, furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionlly substituted with up to two substituents selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety or benzyloxycarbonyl, with the proviso that said R^{11} is always other than unsubstituted phenyl, fluorophenyl, chlorophenyl, bromophenyl or alkylphenyl when said R^1 is unsubstituted phenyl, pyrrolyl or thienyl and Ar is other than thienyl;

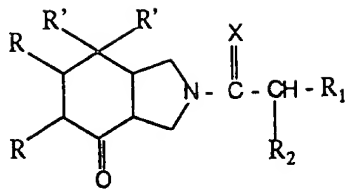
for example cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydryl-quinuclidine;

WO 91/18899 i.e. compounds of the formula:



wherein R^1 is hydrogen or (C_1-C_6)alkyl; R^2 is phenyl, pyridyl, thienyl or furyl, and R^2 may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, chloro, fluoro, bromo, iodo and trifluoromethyl; R^3 is phenyl, naphthyl, pyridyl, thienyl or furyl, and R^3 may optionally be substituted with one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, chloro, fluoro, bromo, iodo and trifluoromethyl; and the pharmaceutically acceptable salts of such compounds;

EP 0429366 i.e. isoindoline derivatives of the formula:



in the (3aR, 7aR) and (3aRS, 7aRS) forms, and mixtures and salts thereof where

R represents hydrogen, or together R and R form a bond;

R' are identical and represent phenyl, optionally substituted by halogen or methyl in position 2 or 3;

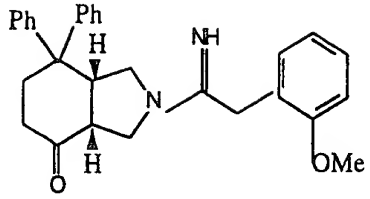
X represents O, S or NR_3;

R_3 represents hydrogen, C_{1-12}alkyl (optionally substituted by one or more carboxy, dialkylamino, acylamino, alkoxycarbonyl, alkoxycarbonylamino, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl (where the alkyl portions of these radicals may contain a dialkylamino or phenyl substituent), phenyl (optionally substituted by halogen, alkyl, alkoxy or dialkylamino), naphthyl, thienyl, furyl, pyridyl or imidazolyl); or dialkylamino;

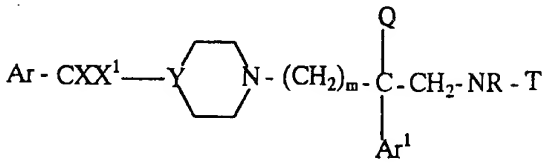
R_1 represents phenyl (optionally substituted by 1 or more halogen, OH, alkyl (optionally substituted by halogen, amino, alkylamino or dialkylamino), alkoxy or alkylthio (optionally substituted by OH or dialkylamino of which the alkyl portions may form a 5- to 6-membered heterocycle which can contain another O, S or N heteroatom), or substituted by amino, alkylamino or dialkylamino); or R_1 is a cyclohexadienyl, naphthyl or (un)saturated 5-9C mono or polycyclic heterocyclyl having one or more O, N or S heteroatoms;

R_2 represents H, halogen, OH, alkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkylthio, acyloxy, carboxy, alkoxycarbonyl, dialkylaminoalkoxycarbonyl, benxyloxycarbonyl, amino, acylamino or alkoxycarbonylamino; the various alkyl and acyl groups being straight or branched and of 1-4C atoms;

for example



EP 0428434 i.e. 1,4-diaralkylpiperidine and piperazine derivatives of the formula:



where

m = 1-3;

Ar, Ar^1 represents thienyl; phenyl optionally mono- or disubstituted by halogen, 1-3C alkyl, CF_3, 1-3C alkoxy, OH or methylenedioxy; or imidazolyl; or Ar^1 may also be benzothienyl optionally substituted by halogen; naphthyl optionally substituted by halogen; biphenylyl; or indolyl optionally substituted by benzyl;

X^1 represents hydrogen or OH;

Y represents N or CX^{11};

X and X^{11} represent hydrogen; or X^1 or X^{11} is a bond; or X and X^1 represent O or $NO(CH_2)pAm$;

p represents 2 or 3;

Am represents di(1-4Calkyl)amino;

Q represents hydrogen, 1-4Calkyl or $(CH_2)qAm$;

q represents 2 or 3;

Am represents piperidino, 4-benzylpiperidino or di(1-4Calkyl)amino;

R represents hydrogen, methyl or $(CH_2)_nL$;

L represents hydrogen or NH_2;

n represents 2-6;

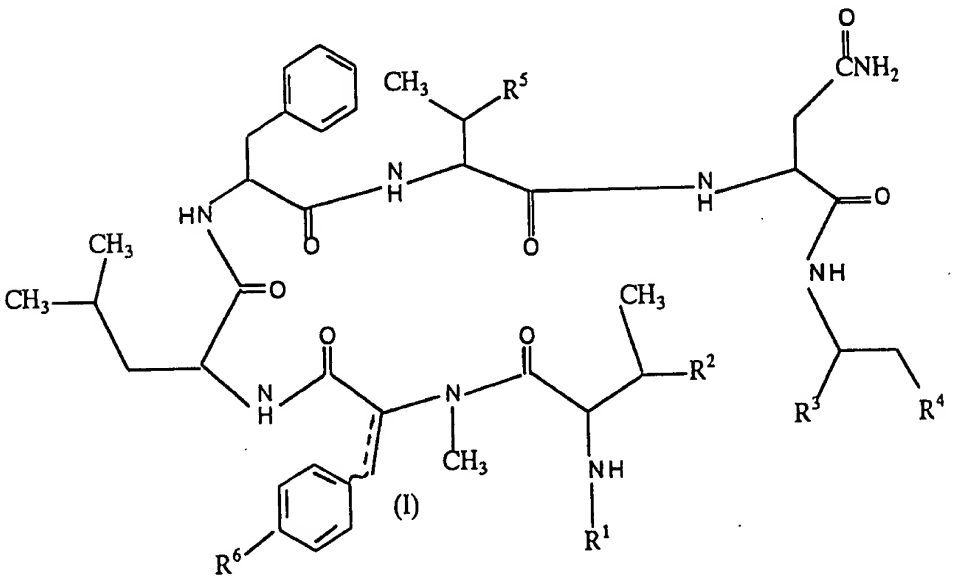
T represents COM, COOM, CONHM or CSNHM;

M represents hydrogen, 1-6C alkyl, phenyl(1-3C)alkyl (optionally ring-substituted by halogen, OH, 1-4C alkoxy or 1-4C alkyl), pyridyl(1-3C)alkyl, naphthyl(1-3C)alkyl, pyridylthio(1-3C)alkyl,

CH181

styryl, 1-methyl-2-imidazolylthio(1-3C) alkyl, 1-oxo-3-phenyl-2-indanyl or optionally substituted aryl or heteroaryl; and optical isomers and acid addition salts thereof;

EP 0336230 i.e. compounds of the formula:



(I)

wherein

R^1 is hydrogen or an acyl group;

R^2 is hydroxy and

R^3 is carboxy or protected carboxy, or

R^2 and R^3 are linked together to represent a group of the formula: -O-C(O);

R^4 is hydroxy or protected hydroxy;

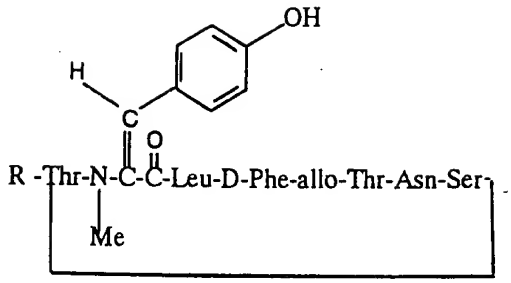
R^5 is hydroxy or protected hydroxy;

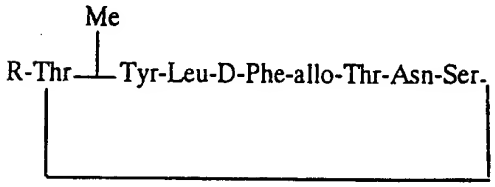
R^6 is hydroxy, protected hydroxy or lower alkoxy;

and

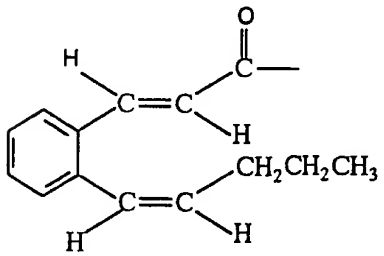
---- is a single bond or a double bond;

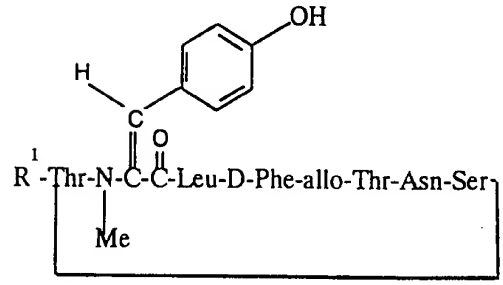
for example



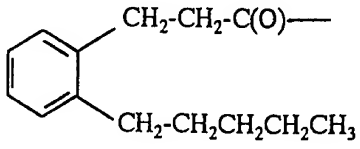


R-:

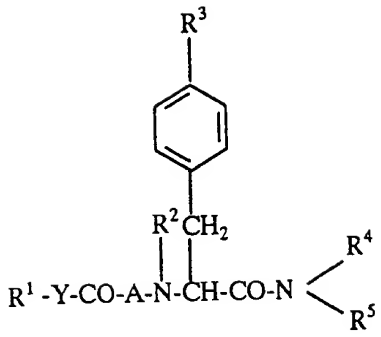




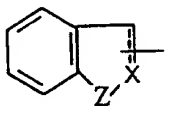
R^1-:



EP 0394989 i.e. compounds of the formula



wherein R^1 is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula:



wherein the symbol of a line and dotted line is a single bond or double bond,

X is CH or N, and

Z is O, S or NH,

each of which may have suitable substituents(s);

R^2 is hydrogen or lower alkyl;

R^3 is hydroxy;

R^4 is lower alkyl which may have suitable substituent(s), and

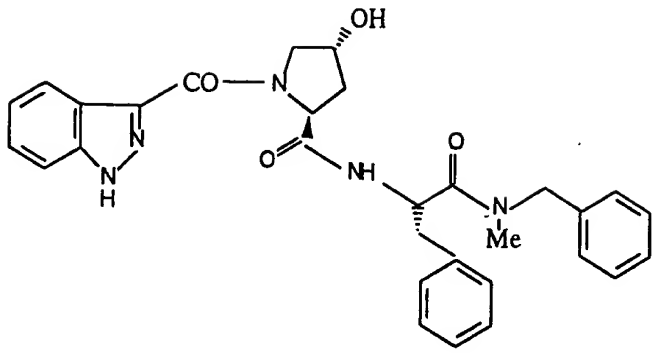
R^5 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

R^4 and R^5 are linked together to form benzene-condensed lower alkylene;

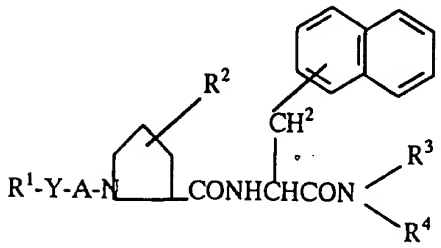
A is an amino acid residue excepting D-Trp, which may have suitable substituent(s); and

Y is a bond, lower alkylene or lower alkenylene;

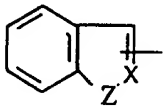
for example



EP 0443132 i.e. compounds of the formula:



wherein R^1 is aryl, or a group of the formula:



wherein

X is CH or N, and

Z is O or N-R^5, in which R^5 is hydrogen or lower alkyl,

R^2 is hydroxy or lower alkoxy,

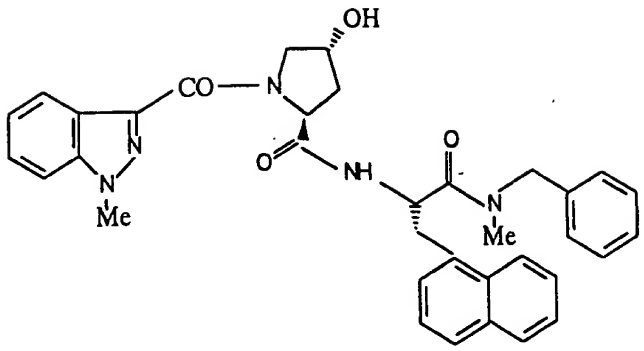
R^3 is hydrogen lower alkyl which may have suitable substituent(s),

R^4 is ar(lower)alkyl which may have suitable substituent(s),

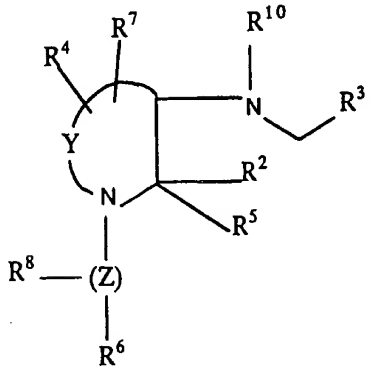
A is carbonyl or sulfonyl, and

Y is bond, or lower alkenylene;

for example



EP 0436334 i.e. compounds of the formula:



wherein Y is $(CH_2)_n$ wherein n is an integer from 1 to 4, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4 and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7;

Z is $(CH_2)_m$ wherein m is an integer from 0 to 6, and wherein any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, (C_1-C_4)alkoxy or fluoro;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the CH_2 groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulfur; aryl

selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)-alkyl, benzhydryl and benzyl, wherein each of said aryl, heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)-alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(O)-, (C_1-C_6)alkyl-O-C(O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(O)-O-, (C_1-C_6)alkyl-C(O)-, (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(O)-, (C_1-C_6)alkyl-C(O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CONH-(C_1-$_6$)alkyl, (C_1-C_6)-alkyl-CONH-(C_1-C_6)alkyl, NHC(O)H and -NHC(O)-(C_1-C_6) alkyl;

and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^5 is hydrogen, phenyl or (C_1-C_6) alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated ring having from 3 to 7 carbon atoms wherein one of the CH_2 groups in said ring may optionally be replaced by oxygen, NH or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteoaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl; tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of the (CH_2) groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulfur;

wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6) alkylamino, -CONH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(O)-NH-(C_1-C_6)alkyl, -NHC(O)H and -NHC(O)-(C_1-C_6)alkyl; and

R^4 and R^7 are each independently selected from hydroxy, hydrogen, halo, amino, oxo, cyano, methylene, hydroxymethyl, halomethyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6) alkoxy,

(C_1-C_6)alkyl-O-C(O)-, (C_1-C_6)alkyl-O-C(O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(O), (C_1-C_6)alkyl-C-(O)-(C_1-C_6)alkyl-O, (C_1-C_6)alkyl-C(O), (C_1-C_6)alkyl-C(O)-(C_1-C_6)alkyl-,

and the radicals set forth in the definition of R^2, R^6 is $NHC(O)R^9$, $-NHCH_2R^9$, SO_2R^9 or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^8 is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl(C_1-C_6)alkyl;

with the proviso that (a) when m is 0, R^8 is absent, (b) when R^4, R^6, R^7 or R^8 is as defined in R^2, it cannot form, together with the carbon to which it is attached, a ring with R^5, and (C) when R^4 and R^7 are attached to the same carbon atom, then either each of R^4 and R^7 is independently selected from hydrogen, fluoro and (C_1-C_6) alkyl, or R^4 and R^7, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; and pharmaceutically acceptable acid addition salts thereof;

in particular cis-3-(2-methoxybenzylamino)-2-phenyl piperidine.

The tachykinin antagonists may be administered as the raw chemical but the active ingredients are preferably presented as a pharmaceutical formulation. Suitable pharmaceutical formulations are described in the above referenced patent specifications.

Suitable dose ranges are also described in the above referenced patent specifications, that is to say that for use as anti-emetics the compounds may be used at doses appropriate for other conditions for which tachykinin antagonists are known to be useful. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A

suitable dose range is for example 0.1mg/kg to about 400mg/kg bodyweight per day.

The tachykinin antagonists may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the tachykinin antagonists may be administered in combination with a systemic anti-inflammatory corticosteroid such as methyl prednisolone or dexamethasone, or a $5HT_3$ antagonist such as ondansetron, granisetron or metoclopramide.

Biological Data

The anti-emetic activity of the test compound (±) cis-3-(2-methoxybenzylamino)-2-phenyl piperidine was demonstrated by its ability to inhibit cisplatin-induced emesis in the ferrett.

In this model of emesis the onset of retching and vomiting occurs approximately 1 hour after the administration of cisplatin (200mg/m^2 i.p.). At the first retch in response to cisplatin, the test compound was administered (e.g. i.p., p.o., i.v., s.c., i.c.v.) and its effect on emesis determined by comparison with appropriate controls (e.g.water).

The test compound exhibited anti-emetic activity when administered at a dose of 3 mg/kg i.p.